Reaction of Nucleosides with Lead Tetra-acetate: Facile Formation of Cyclonucleosides

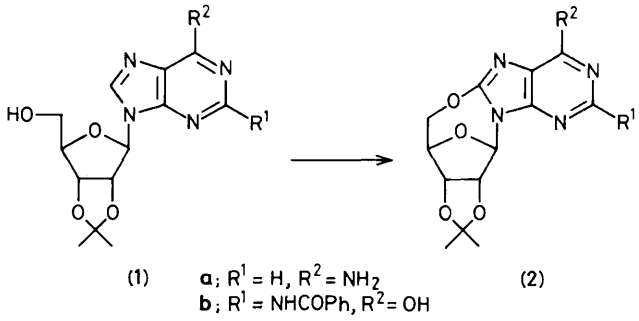
Keiji Kameyama, Magoichi Sako, Kosaku Hirota, and Yoshifumi Maki*

Gifu Pharmaceutical University, 6–1, Mitahora-higashi 5 Chome, Gifu 502, Japan

Reaction of appropriately protected purine nucleosides (adenosine and guanosine) with lead tetra-acetate results in the formation of the corresponding 5′-*O*,8-cyclopurine nucleosides (**2**), whereas that of the protected pyrimidine nucleosides (uridine and cytidine) gives predominantly 5-acetoxy-5′-*O*,6-cyclo-5,6-dihydrouridine (**4**).

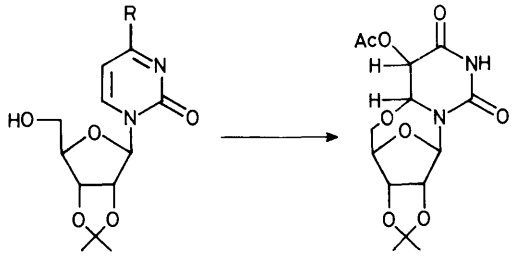
There is much interest in various types of purine and pyrimidine cyclonucleosides because they can be utilised as a tool for conformational studies of nucleosides and as key intermediates in the synthesis of many biologically active substances.[1,2]

We report here a new simple method for the preparation of 5′-*O*,8-cyclopurine nucleosides (**2**) and the hitherto unknown 5-acetoxy-5′-*O*,6-cyclo-5,6-dihydrouridine (**4**), which involves intramolecular oxidative cyclisation of appropriately protected nucleosides (**1**) and (**3**) induced by lead tetra-acetate (LTA). The present reaction also has interesting mechanistic implications.



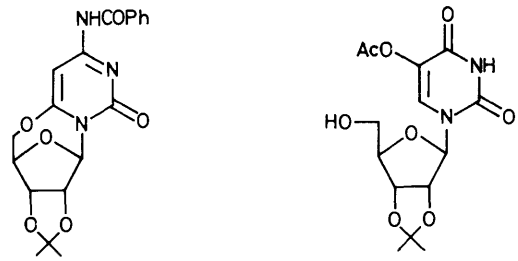
(1) a; R^1 = H, R^2 = NH_2
b; R^1 = NHCOPh, R^2 = OH

(2)



(3)
a; R = OH
b; R = NHCOPh

(4)



(5)

(6)

A mixture of 2′,3′-*O*-isopropylideneadenosine (**1a**) (3 mmol) and LTA (6 mmol) in dry benzene (50 ml) was heated under reflux for 2 h. After cooling, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was chromatographed over silica gel. Recrystallisation of the crude product, eluted with chloroform–methanol (98:2), from aqueous ethanol gave 5′-*O*,8-cyclo-2′,3′-*O*-isopropylideneadenosine (**2a**)† in 90% yield. The cyclonucleoside (**2a**) thus obtained from the protected adenosine (**1a**) by the one step procedure was identical in every respect with an authentic sample prepared by base-catalysed cyclisation of 2′,3′-*O*-isopropylidene-8-bromoadenosine.[3]

The oxidative cyclisation of 2′,3′-*O*-isopropylideneguanosine with LTA did not occur under the conditions examined. Its N^2-benzoyl derivative (**1b**), however, resulted in the formation of the corresponding 5′-*O*,8-cycloguanosine (**2b**), m.p. >300 °C, in 40% yield using the same method as in the formation of (**1a**). The structure of (**2b**) was confirmed by comparison with a sample obtained by benzoylation of 5′-*O*,8-cyclo-2′,3′-*O*-isopropylideneguanosine.[4]

The reaction of the protected pyrimidine nucleosides (**3a**, **b**) with LTA proceeded in a manner different from that of the purine nucleosides (**1a**, **b**) to give a novel type of a cyclonucleoside (**4**).

Treatment of 2′,3′-*O*-isopropylideneuridine (**3a**) with LTA in a similar manner to (**1a**, **b**) gave 5-acetoxy-5′-*O*,6-cyclo-5,6-dihydro-2′,3′-*O*-isopropylideneuridine (**4**), m.p. 188—190 °C, in 92% yield. The structure of (**4**) was determined from its spectral data and chemical conversion. For example, no characteristic u.v. absorption of the uracil ring was observed. The ^{1}H n.m.r. spectrum of (**4**) (60 MHz, in $CDCl_3$) showed a methyl proton signal at δ 2.18 (s, 3H, $COCH_3$) and two methine proton signals at δ 4.97 and 5.44 (each 1H, each d, *J* 9.2 Hz, 5-H and 6-H) in addition to signals assignable to an imido proton [δ 9.08 (1H, br)] and protons in the protected sugar portion. Heating of (**4**) in dimethylformamide gave with ease 5-acetoxy-2′,3′-*O*-isopropylideneuridine (**6**) which was identified by comparison with an authentic sample.[5] Although at present the stereochemistry of (**4**) is uncertain, its stereospecific formation is interesting from the mechanistic viewpoint.

In spite of many attempts under various conditions, isolation of the products in the reaction of 2′,3′-*O*-isopropylidenecytidine with LTA was unsuccessful. However, when N^4-benzoyl-2′,3′-*O*-isopropylidenecytidine (**3b**) was allowed to react with LTA in acetonitrile at room temperature for 5 h, (**4**) (50%) and 4-benzoylamino-5′-*O*,6-cyclo-2′,3′-*O*-isopropylidinecytidine (**5**) (15%, m.p. 120—122 °C) were obtained. The structure of (**5**) was supported by its spectral data and debenzoylation using zinc bromide as a catalyst in methanol[6] to give 5′-*O*,6-cyclo-2′,3′-*O*-isopropylidenecytidine.[7] The ^{1}H n.m.r. spectrum of (**5**) (60 MHz, in $CDCl_3$) showed a 5-H signal at δ 7.19 (s, 1H) and an amido proton signal at δ 9.23 (br, 1H) in addition to signals assignable to protons in the protected sugar portion.

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† The cyclonucleosides described here gave satisfactory microanalytical results and spectral data consistent with their structures.

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